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EXAMINER	
GANGLE, BRIAN J	

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1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,216	KINGSMORE ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-23 and 96-108* is/are pending in the application.

4a) Of the above claim(s) *5,6,9-18,20-23 and 96-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/2008, 7/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 6/30/2008 is acknowledged. Claims 1-6, 8-23 and 96-108 are pending. Claims 5-6, 9-18, 20-23, and 96-108 are withdrawn as being drawn to non-elected inventions. Claims 1-4, 8, and 19 are currently under examination. It is noted that applicant filed a response including an amendment to the specification on 2/22/2008. However, this amendment was not entered, as set forth in the notice of non-compliance sent to applicant on 5/29/2008.

Election/Restrictions

Applicant affirms the telephonic election of MPIF-1 and TNF-R1 made on 7/26/2007 and traverses this restriction. The traversal is on the grounds that claim 1 is a linking claim that links the other pending claims in the application. Applicant asserts that, because of this, examination of claim 1 should not be limited to the combination of MPIF-1 and TNF-R1 and asserts that, should claim 1 be allowable, the restriction between the linked inventions must be withdrawn.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant correctly asserts that claim 1 is a linking claim that links the pending claims. As a generic claim, claim 1 was considered to its full breadth and not found allowable; therefore the restriction is proper.

Information Disclosure Statement

The information disclosure statements filed on 2/22/2008 and 7/21/2008 are acknowledged. Initialed copies are enclosed.

Objections Withdrawn

The objection to claims 1-4 and 19 because the claims are drawn, in part, to non-elected subject matter is withdrawn upon reconsideration.

Objections Maintained

Drawings

The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5), because they include the following reference character(s) not mentioned in the description: 5A-5E and 6A-6E, is maintained for the reasons set forth in the previous office action. As noted above, the amendment filed on 2/22/2008 was not entered. This objection will be withdrawn if said amendment is properly filed with a compliant response.

Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 9, is maintained for the reasons set forth previously. Applicant has not addressed this objection. There are multiple references to Fig. 9 on pages 22 and 23 in the specification.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

New Objections

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figures 11, 12, and 14. Reference is made to Figures 11, 12, and 14 on pages 19, 34, and 30, respectively. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

It is noted that the cited occurrences are only exemplary and applicant should review the entire specification to correct any other improper reference to the drawings.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-4, 8, and 19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. That the examiner has not examined the claims as written. Applicant refers to a sentence in the office action which states that the claims are drawn to methods comprising determining the concentration of MPIF-1 and TNF-R1.

2. That the definition of sepsis in the art is consistent with the definition provided in the specification. Applicant refers to a definition of sepsis provided by Bone *et al.* and asserts that infections such as influenza and roseola can be within the definition of sepsis.

3. That the specification specifically states that MPIF-1 may be used individually or together with other biomarkers in marker panels to provide a prognostic panel for diagnosis of sepsis.

4. That the examiner has "taken issue with the fact that MPIF-1 and TNFR1 might be elevated in conditions other than sepsis, asserting that this makes these markers 'unacceptable for the diagnosis of sepsis.'" Applicant asserts that it is not clear what scientific basis the examiner based this assertion on, "as no scientific reasoning or reference is provided in support."

5. That virtually all diagnostic tests lack the type of specificity the examiner is implying is necessary. Applicant asserts that it is not necessary to have "specific markers" for a particular disease or condition in order to practice the claimed methods without undue experimentation and with a reasonable level of predictability.

6. That there are multiple tests that are approved by the FDA that use markers for various diseases which are not "specific markers" for said diseases. Applicant discusses procalcitonin, which is elevated in various non-infectious conditions but is an FDA-approved test for use in evaluation of sepsis.

Applicant states that D-dimer is an "FDA-approved test for use in the evaluation of pulmonary embolism" even though, Indik *et al.* state that the specificity of DD assays is expected to be low because D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis.

Applicant states that assays that detect B-type natriuretic peptide are FDA-approved for use in the diagnosis of heart failure, but are also approved as a risk marker in acute coronary syndromes.

Applicant states that the prostate-specific antigen test is routinely used by artisans for initial diagnosis and screening for prostate cancer despite the fact that it is elevated in conditions such as benign prostate enlargement, inflammation, and infection.

Applicant states that CRP is a marker that is elevated in numerous inflammatory processes including cancer, connective tissue disease, heart attack, etc., and states that while only

a fraction of subjects having an increased CRP level will have any of these conditions, but CRP tests are FDA approved and routinely used by clinicians.

7. That the skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis of patients and is prepared to perform the required studies to establish the performance characteristics for particular patient populations seen at each institution. Applicant also asserts that ones a biomarker has been identified, the remaining experimentation is routine. Applicant also asserts that routine experimentation can provide a "cutoff" value that provides the desired sensitivity and specificity.

8. That the specification demonstrates that MPIF-1 and TNF-R1 are significantly elevated in patients with sepsis. Applicant refers to paragraphs 0086, 00196, and Table 7 to support this contention.

9. That the examiner, in stating that the fact that severe sepsis was required for TNF-R1 levels to be significantly raised, is implying that a marker must be 100% sensitive to meet the enablement requirement. Applicant refers again to procalcitonin to suggest that markers which are not 100% specific and 100% sensitive are useful as diagnostics. Applicant refers to US patent 5,639,617, stating that it relates to the use of procalcitonin in the diagnosis of sepsis. Applicant also argues that, based on an FDA report, results of procalcitonin measurements largely overlap for sepsis patients and non-infected controls until sepsis becomes more severe.

10. That the methods to be followed are routine and the only issue that remains is an identification of which markers apply to sepsis diagnosis, which is solved by the present specification and claims.

11. That the present application provides exemplary data for MPIF-1 and TNF-R1.

12. That the examiner's comments concerning the breadth of the definition of sepsis demonstrate a lack of understanding of the knowledge available in the art.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, contrary to applicant's assertion, the examiner has examined the instant claims as written and has discussed the full breadth of the claims. Applicant has referred to a sentence from the previous office action that summarizes the claims and which recites both MPIF-1 and TNF-R1. However, applicant has neglected to consider the very next sentence which states "For claims 1-4 and 8, an elevated concentration of MPIF-1 in the test sample,

relative to the reference concentration , is indicative of the presence of sepsis; and for claim 19, an elevated concentration of both MPIF-1 and TNF-R1 is indicative of sepsis." This clearly indicates that the examiner has considered claims 1-4 and 8 as requiring only the measurement of MPIF-1. Moreover, throughout the rejection, MPIF-1 and TNF-R1 and their respective relationships with sepsis were discussed separately.

Regarding argument 2, while applicant has referred to *a* definition of sepsis in the art by Bone *et al.*, this is hardly the *only* definition, or even the consensus definition, of sepsis in the art. Cruse *et al.* (Illustrated Dictionary of Immunology, 2nd edition, CRC Press, 2003, page 539) defines sepsis as a "bloodstream infection that is life threatening and often leads to death." Dorland's Medical Dictionary (http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/seven/000095957.htm, accessed 10/6/2008) defines sepsis as "the presence in the blood or other tissues of pathogenic microorganisms or their toxins." The Online Medical Dictionary (http://cancerweb.ncl.ac.uk/cgi-bin/omd?sepsis, accessed 10/6/2008) defines sepsis as "the presence of organisms in the blood." The National Institutes of Health (Medical Encyclopedia, http://www.nlm.nih.gov/medlineplus/ency/article/000666.htm, accessed 10/6/2008) defines sepsis as "a severe illness caused by overwhelming infection of the bloodstream by toxin-producing bacteria." As evidenced by the above definitions (which were published well after Bone *et al.*), the art continues to lack a consistent definition of sepsis. In fact, Poeze *et al.* (Critical Care, 8:R409-R413, 2004) stated that the definition provided by Bone *et al.* has not found unequivocal acceptance (page R409, column 2). Only 22% of intensivists and 5% of other physicians gave the definition set forth by Bone *et al.* as the definition of sepsis and fewer than one-fifth of physicians agreed on any one definition (page R411, column 1, paragraph 3). It must be stated here that the examiner does not disagree with the definition of sepsis provided in the specification. As stated in the MPEP, applicant is free to be his or her own lexicographer and thus may define sepsis in any way they wish. If, as applicant states in their argument, they wish a flu infection to be considered sepsis, it is their right. However, the lack of a consensus in the art with regard to what is (or is not) sepsis, is relevant to the discussion of enablement. First, because the lack of consensus shows that the state of the art is inconsistent and second, because applicant's definition is so broad as to include a flu infection, applicant's

method must be able to diagnose someone infected with the flu virus (or any other appropriate infection) as having sepsis. The specification does not provide any guidance that would lead one to believe that this would occur. Furthermore, while applicant may define someone having the flu as being septic, common sense tells us that the vast majority of physicians would not agree.

Regarding argument 3, the claims do not recite a method where MPIF-1 is used "in marker panels to provide a prognostic panel for diagnosis of sepsis." According to the claims, "an elevated concentration of MPIF-1 in the test sample relative to the reference concentration is indicative of the presence of sepsis in the human." There is no mention in the claims of use in a "prognostic panel." Furthermore, merely stating something does not make it so. While the specification may state that MPIF-1 may be used in this manner, the specification also provides evidence that an association between increased MPIF-1 levels and sepsis is unpredictable.

Regarding argument 4, the examiner did not take issue with the fact that MPIF-1 and TNF-R1 *might* be elevated in conditions other than sepsis. The examiner has taken issue with the fact that MPIF-1 and TNF-R1 *are* elevated in conditions other than sepsis. Applicant states that no scientific basis or references have been provided to support the examiner's reasoning. This is entirely incorrect. The previous office action discusses references by Kimura *et al.*, Slotwinski *et al.*, two articles by Dollner *et al.*, and applicant's own specification. The scientific reasoning and findings of the above references was discussed previously at length. These references show that MPIF-1 and TNF-R1 levels are not predictably correlated with sepsis. In addition to the above references, other authors have also shown MPIF-1 in particular to be elevated in conditions other than sepsis. For example, Hurst *et al.* (Am. J. Respir. Crit. Care Med., 174:867-874, 2006) showed that MPIF-1 was elevated in patients with chronic obstructive pulmonary disease. As for the reasoning that MPIF-1 and TNF-R1 are unacceptable for the diagnosis of sepsis, the art has shown that these cytokines are elevated in samples from patients who do not have sepsis. According to the claims, an elevated concentration of MPIF-1 *is indicative of the presence of sepsis*. As shown in the art, this is simply not true.

Regarding argument 5, the examiner has not required any particular "type of specificity." What is required is that the claimed method be operable. As stated above, elevated levels of MPIF-1 and TNF-R1 are not indicative of the presence of sepsis and applicant's own specification shows that the relationship between sepsis and these levels is unpredictable.

Regarding argument 6, whether or not the FDA has approved various tests for particular uses is not at issue. The regulatory requirements set forth by the FDA for a specific condition do not impact whether or not elevated MPIF-1 and TNF-R1 levels are indicative of sepsis, as is required by the claims. Furthermore, as discussed below, if one reads the details of the references, each of the examples used by applicant only further support the examiner's position.

As applicant states procalcitonin is an FDA-approved test *for use in the evaluation of sepsis*. According to the FDA summary, the test is "intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock" (page 10). This does not, in any way, imply that one can use procalcitonin alone to diagnose sepsis or that elevated levels of procalcitonin are indicative of sepsis.

With regard to D-dimers, again, applicant again correctly states that it is *for use in the evaluation of* pulmonary embolism. Indik *et al.* state that, because specificity is low, "the potential value of a DD test lies, therefore, in its ability to exclude PE" (page 262, column 2, paragraph 3). This means that one could not diagnose someone as having pulmonary embolism purely on the basis of a DD test.

With regard to BNP, applicant is implying that elevated BNP levels allow one to diagnose heart failure and acute coronary syndrome. However, if one reads the reference that applicant supplied, it states that "the test is intended to be used as an aid in the diagnosis and assessment of severity of congestive heart failure." The most important part of that sentence is the statement is that the test is intended *to be used as an aid*. Therefore the test, in and of itself, does not provide a diagnosis of heart failure. In fact the reference also states, on page 3, "the Triage BNP Test should not be used as absolute evidence for CHF. The results should be interpreted along with clinical findings and other laboratory test results."

Contrary to applicant's assertion, the prostate-specific antigen test is not used to diagnose prostate cancer. This is for precisely the reasons that the instantly claimed methods are not operable. As stated in the NIH website applicant refers to, greater-than-normal PSA levels may indicate: benign prostatic hypertrophy, prostate cancer, prostatis, prostate infection, urinary tract infection, recent urinary catheterization, or recent urinary tract operation. Therefore, increased levels of PSA do not indicate that one has prostate cancer. The website also states "a high PSA

level only identifies patients at higher risk of having prostate cancer." It is well known that the PSA test is useful for *initial screening* for prostate cancer and no physician would recommend treatment of prostate cancer based on an abnormal PSA test.

As with the other markers mentioned by applicant, elevated CRP levels are not indicative of any particular disease. This is also supported by applicant's reference, which states that a positive test means you have inflammation in the body, possibly caused by cancer, connective tissue disease, infection, lupus, and rheumatoid arthritis, among others. Clearly, while measurement of CRP levels is useful in the evaluation of disease, these levels are not indicative of any particular disease and therefore cannot serve to diagnose any particular disease.

Each of the markers cited by applicant is useful in the diagnosis of disease, but none of them are diagnostic of any disease, as a positive result for any of them is not indicative of the presence of a given disease. The is precisely the situation with MPIF-1 and TNF-R1. They may be useful tools, in combination with other tests, to aid in the diagnosis of sepsis, but elevated levels are not indicative of sepsis, particularly when one considers that applicant's definition of sepsis includes conditions such as flu infection. If one were to practice the claimed method steps and find elevated levels of MPIF-1, one would not know whether the subject had sepsis or whether they had chronic obstructive pulmonary disease.

Regarding argument 7, applicant is describing a skilled artisan that is unlikely to exist. If the skilled had extensive experience with the clinical use of biomarker tests for diagnosis of patients, said artisan must be a physician that works with patients rather than simply a researcher. Physicians in clinical practice would only be using FDA-approved diagnostic kits and are not generally equipped to perform validation studies with new diagnostic kits. In addition, applicant appears to be suggesting that validation studies must be performed for each different patient population at each different institution. Studies using human test subjects are highly complicated and time consuming and are no simple matter. Therefore, applicant is suggesting that skilled artisans who do not agree on a definition of sepsis and who spend their time diagnosing patients as well as performing statistical evaluations in research laboratories, should perform testing on human subjects for every type of sample for each different patient population at each different institution, to study markers that are unpredictably related to sepsis as well as related to other conditions, guided by a specification that shows conflicting results. This constitutes undue

experimentation. With regard to the "cutoff" value, there is no such value recited in the claims. Claim 1 states "an elevated concentration of MPIF-1 in the test sample relative to the reference concentration is indicative of the presence of sepsis in the human."

Regarding argument 8, despite applicant's assertion, the specification does not demonstrate with any predictability that MPIF-1 and TNF-R1 are significantly elevated in patients with sepsis. When considering enablement, the entirety of the evidence must be considered, not just 0086, 00196, and Table 7. These paragraphs and table do suggest that MPIF-1 and TNF-R1 are significantly elevated in patients with sepsis. However, paragraph 0086 shows no data and refers to a figure that does not exist. In addition, paragraph 0196 and Table 7 both refer to study 3. Applicant has neglected to mention studies 1 and 2, where different results were obtained. As discussed previously, TNF-R1 was not identified in either study 1 or 2 as a potential marker for sepsis. In serum samples, MPIF-1 was elevated in sepsis patients, but was not found to be elevated in sepsis patients in study 2. The specification also states that TNF-R1 levels were elevated in trauma patients (page 53). As discussed above, this shows that one cannot use TNF-R1 to diagnose sepsis, as elevated levels are not indicative of sepsis.

Regarding argument 9, the examiner is making no such implication. However, the full scope of the claims must be enabled. The specification seems to prove that TNF-R1 levels are only elevated when patients have severe sepsis. The claims are not limited to the diagnosis of severe sepsis; they encompass sepsis of any severity (even including flu infections), which applicant has not shown leads to elevated levels of TNF-R1.

With regard to US patent 5,639,617, each patent application is considered on it's own merits and the fact that a patent was issued for the use of procalcitonin in diagnosis of sepsis does not bear on the instant use of MPIF-1 and TNF-R1.

With regard to the FDA summary on procalcitonin use, the summary states that the test is "intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock" (page 10). This does not, in any way, imply that one can use procalcitonin alone to diagnose sepsis or that elevated levels of procalcitonin are indicative of sepsis.

Regarding arguments 10 and 11, as discussed above, the specification does not provide evidence that elevated levels of MPIF-1 and TNF-R1 are indicative of sepsis, as is required by the claims.

Regarding argument 12, applicant is free to define the term sepsis in any way they wish. In this case, it has been defined very broadly so as to include conditions that much of the art would not consider as sepsis. This is applicant's right and it not at issue. The definition was brought up because the state of the art is part of the consideration of enablement and it is important to note that the art lacks a consensus definition for the term. As stated above, the definition that applicant has chosen is not the only definition found in the art and while applicant is free to ignore the teachings of the art, this does not suggest that the examiner lacks an understanding of the art.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of diagnosing sepsis in a human subject, comprising determining the concentration of myeloid progenitor inhibitory

factor-1 (MPIF-1) and tumor necrosis factor receptor-1 (TNF-R1) in a sample and comparing said concentration to corresponding reference concentrations, selected to indicate the presence or absence of sepsis, wherein said reference concentration is determined using one or more control samples obtained from one or more human subjects not suffering from sepsis. For claims 1-4 and 8, an elevated concentration of MPIF-1 in the test sample, relative to the reference concentration, is indicative of the presence of sepsis; and for claim 19, an elevated concentration of both MPIF-1 and TNF-R1 is indicative of sepsis.

Breadth of the claims: The claims encompass the detection of sepsis, which is defined in the specification as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation. It is noted that this definition encompasses many conditions and diseases that are not considered sepsis by the art. This includes diseases such as influenza, roseola, as well as conditions associated with trauma and surgery. The method further encompasses samples of all types from humans, including hair and tissue samples other than blood or serum.

Guidance of the specification/The existence of working examples: The specification discloses information about sepsis, which is defined in the specification as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation. The specification teaches that there are multiple biomarkers that have been associated with sepsis, mostly these are cytokines associated with inflammation. Of these cytokines, some information is given on myeloid progenitor inhibitory factor-1 (MPIF-1) and tumor necrosis factor receptor-1 (TNF-R1). MPIF-1 is a cytokine that binds to CCR1. The specification states that there is no literature describing a direct association between MPIF-1 levels and sepsis, which concurs with the examiner's findings. Of TNF-R1, the specification states, "soluble TNF receptor levels were elevated in trauma patients compared to healthy persons. Severe trauma led to enhanced sTNF-R1 levels on scene and on hospital admission." Increased TNF-R1 levels are also associated with sepsis. The specification provides several studies where the levels of various biomarkers were determined in patients with sepsis and compared to those in patients without sepsis. Statistical evaluations of these data are presented

which show conflicting results. Three studies were undertaken to identify suitable biomarkers for the diagnosis of sepsis. For MPIF-1, study 1 showed a significant difference between healthy and septic individuals in both serum and plasma samples. However, study 2 showed the increase only in plasma and not in serum. Also, TNF-R1 was not identified in either study as a potential marker. In study 3, MPIF-R1 was increased in septic individuals, as was TNF-R1. The specification addresses the differences in results by listing the differences between the studies. Studies 1 and 2 were small, involving 6 and 12 patients, respectively; whereas study 3 involved 240 sepsis patients. In study 3, the patients had more severe sepsis than those in studies 1 and 2. In addition, the comparisons in studies 1 and 2 were between healthy patients and septic patients, while in study 3, the comparison was between ill, but non-septic patients and septic patients. Finally, studies 1 and 2 involved plasma and serum samples, while study 3 involved diluted serum.

State of the art: As stated above, there is nothing in the prior art that directly links MPIF-1 levels with sepsis, although it is linked with inflammation. TNF-R1 is linked with sepsis, but also with other conditions. Kimura *et al.* (British J. Surg., 85:1631-1635, 1998) showed that TNF-R1 is produced in response to surgical stress, and may be further enhanced by intraoperative bacterial translocation. They suggest that plasma TNF-R1 concentrations may be predictive of postoperative infectious complications (including peritoneal abscess and pneumonia, which are not necessarily conditions of sepsis) (see Table 1 and page 1634, final paragraph). Dollner *et al.* (Biol. Neonate, 80:41-47, 2001) showed that both neonates suffering from various non-infected conditions (such as respiratory distress, intraventricular haemorrhage, and icterus neonatorum) as well as neonates with infection, had higher TNF-R1 (also known as p55) levels than healthy controls (see Table 3). Doellner *et al.* (Early Human Dev., 52:251-261, 1998) attempted to use serum concentrations of TNF-R1 as a diagnostic indicator of sepsis in neonates. However, they found that the specificity of TNF-R1 concentrations was low. They stated, "our data do not suggest that assessment of sTNFR may improve the accuracy of diagnosing early onset neonatal sepsis compared to using CRP. The usefulness of sTNFR as diagnostic tests for infection later in the neonatal period remains to be elucidated" (page 259, final paragraph). Slotwinski *et al.* (J. Clin. Immunol., 22:289-296, 2002) used TNF-R1 to predict local infective complications after colorectal surgery. Slotwinski *et al.* found that TNF-

R1 was significantly elevated immediately after liver resection, as well as in patients with post-operative complications (page 295, paragraph 1).

It is clear from the art and the specification that both MPIF-1 and TNF-R1 are involved in the inflammatory process. However, both of these cytokines are known to be involved, not just in systemic inflammation, but in local inflammation. The specification does not provide guidance showing the levels of either cytokine that are necessary to for a diagnosis of sepsis, and no means has been provided to differentiate between the increase in cytokines associated with trauma, burns, or other infections and the increase associated with sepsis. In fact, the specification shows that, in two studies, TNF-R1 was not found to be associated with sepsis, while MPIF-1 had a different association with sepsis, depending on the sample source. It is suggested in the specification that TNF-R1 was not identified in studies 1 or 2 because these studies were smaller and because, in study 3, the patients had more severe sepsis than those in studies 1 and 2. However, the fact that severe sepsis was required for TNF-R1 levels to be significantly raised further highlights the fact that increased TNF-R1 levels are unacceptable for the diagnosis of sepsis.

Moreover, applicant's definition of sepsis as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation is very broad. Numerous diseases that would not be considered related to sepsis by those in the art are encompassed by this definition, and there is no evidence whatsoever to link MPIF-1 or TNF-R1 levels with these diseases. For example, both influenza and roseola are viral infections that cause fever and leukopenia. A child with the flu would meet the instant definition of being septic, but would not be considered as such by those in the art, and there is no research that suggests one could use increased levels of MPIF-1 and TNF-R1 to diagnose said child as septic. Finally, all samples from humans are encompassed by claims 1, 8, and 19. As MPIF-1 and TNF-R1 are involved in inflammatory processes, they would be present in samples from local infections, but this would not be indicative of systemic inflammation.

Consequently, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the invention as claimed; therefore the claims are not enabled.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1645

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